Table 2. Area and Color of Target Lesions Before Treatment (Day 1) and after 4 Weeks Treatment: Overall Patient Response

Patient/ lesion number	*Target lesion area (mm^2) Day 1*	*Target lesion area (mm^2) Week 4*	*Decrease total target lesion area (%) Week 4*	*Lesion color Day 1*	*Lesion color Week 4*	*Tumor symptoms Day 1*	*Tumor symptoms Week 4*
WEB/1	100	25	74	Purple	Pale pink	Round, firm	Flatter
WEB/3	380	100		Purple	Pale pink	Firm	Flatter
DMS/2	400	324	22	Purple	Very pale pink	Flat	Flat
DMS/3	500	360		Purple	Pale pink	Flat	Flat
DMS/4	100	100		Purple	Pale pink	Flat	Flat
D-D/1	12	1	83	Deep red	Pale pink	Soft	Flat
D-D/2	16	4		Deep red	Pale pink	Soft	Soft, flat
D-D4	25	4		Deep burgundy	Pale pinkish-tan	Soft, slightly raised	Soft, slightly raised
CWK/1	170	170	0	Deep burgundy	Pink	Soft, flat	Soft, flat
CKW/2	289	289		Deep burgundy	Pink	Soft, flat	Soft, flat
CKW/3	121	121		Deep burgundy	Pink	Soft, flat	Soft, flat
SHC/6	198	160	19	Purple	Tan	Firm, pain, edema	Less pain and edema
SHC/7	500	360		Purple	Tan	Firm, pain, edema	
SHC/8	1200	1020		Purple	Tan	Firm, pain, edema	
TLM/5	20	20	0	Pink	Lighter pink	Soft	Softer/ flatter
TLM/6	250	250		Pink	Lighter pink	Firm	Softer/ flatter
TLM/7	360	360		Pink	Lighter pink	Soft	Softer/ flatter
JTG/1	1216	1216	0	Light blue	Pale blue	Soft/flat	Soft/flat
JTG/2	360	360		Pinkish-blue	Pinkish-blue	Soft/flat	Soft/flat
JTG/3	200	200		Pink	Pink	Soft/flat	Soft/flat
TEM/4	25	25	0	Purple	Pale purple	Flat	Flat, soft
TEM/7	120	120	0	Purple	Pale purple	Hard	Soft
TEM/10	1216	1216		Purple	Pale purple	Hard	Soft
WBL/1	450	450	0	Deep-pink	Pink	Firm	Soft, less painful
WBL/2	204	204		Purple	Pinkish-purple	Firm	Soft, less painful
WBL/3	680	680		Purple	Purple, fading	Firm	Softer, less painful
LMK/1	100	56	35	Deep purple	Brown/ yellow	Nodular, firm, round	Firm, round
LMK/2	25	25		Deep purple	Brown/ yellow	Firm, flat	Firm, flat

area by Day 28 at which time it was described as firm and round. Nine lesions that were described as round or firm at study entry (baseline) became flatter and/or softer by the 28-day visit.

Results from extended use protocol

Nine of the 10 patients continued to treat KS lesions with docosanol 10% cream at least 8 weeks into the extended treatment period. One patient (TLM) withdrew from the extended protocol study prior to a follow-up visit. The maximum time of treatment in the extended protocol was 35 weeks. No progression of target lesions was observed, and all patients remained free of signs of visceral disease at their last visit.

In the patients who had a partial response within 28 days of initiating treatment, improvement persisted or continued during extended use as summarized in Table 3. After 14 weeks of treatment the >70% reduction in total lesion area observed in patients WEB and D-D had persisted or further improved. One additional patient, CKW, whose target lesions failed to respond within 28 days, manifested a 52% reduction in total target lesion area after 20 weeks of treatment.

Patient SHC, who had experienced a 16% reduction in lesion area and a loss of lesion color after 28 days, displayed a 42% reduction in total target lesion area by Week 26. By Week 35 the three target lesions (originally 200 to 1200 mm^2, swollen, and painful) were reported by the investigator to be no longer

TABLE 3. SUMMARY OF EXTENDED PROTOCOL RESULTS

Patient	*Decrease at 4 weeks*[a] *(%)*	*Patient response at 4 weeks*	*Total weeks on study*	*Decrease in extended protocol*[a] *(%)*	*Patient response in extended protocol*
WEB	74	Partial	10	74	Partial
DMS	22	Stable	11	18	Stable
D-D	83	Partial	12	92[b]	Partial
CKW	0	Stable	18	52	Partial
SHC	16	Stable	26	42	
			35	100	Partial[c]
TLM	0	Stable	4	Lost to follow-up	—
JTG	0	Stable	12	0	Stable
TEM	0	Stable	12	0	Stable
WBL	0	Stable	12	0	Stable
LMK	35	Stable	13	35	Stable

[a]Decrease in total target lesion area (%).
[b]Two target lesions were no longer visible.
[c]Biopsy of site of one target lesion showed histology suggestive of Kaposi's sarcoma, early patch stage.

visible. Histopathological evaluation of a biopsy sample from the site of one of the target lesions (Fig. 1C) revealed "features suggestive of Kaposi's sarcoma; early-patch-stage" and clinical correlation was advised. Because of the histopathological finding, the patient was classified as having a partial—not a complete—response.

Safety assessment

All 13 patients were assessed for safety and tolerability. Treatment with docosanol 10% cream was well tolerated. No patient reported the occurrence of any localized or systemic adverse events related to drug treatment. There was one discontinuation due to a serious adverse event unrelated to drug treatment (AIDS-related hospitalization). Clinical laboratory findings were judged to be nontreatment related. Treatment compliance in the study was high as determined by patient diaries and returned medication tubes.

DISCUSSION

In this pilot clinical study, reduced symptoms and evidence of disease regression were observed following treatment of KS lesions in HIV-positive patients with the topical antiherpes drug docosanol 10% cream. The study was proposed and conducted based on the broad spectrum of antiviral activity exhibited by docosanol in laboratory studies, its efficacy in the treatment of recurrent oral herpes simplex infections, and on the infectious etiology of KS in HIV-1-infected patients. Target lesions in treated patients exhibited reduced KS lesion area, a lightening of lesion color associated with the disease, and reduced lesion-associated edema and pain.

Two of 10 patients exhibited a PR in the original protocol and an additional two patients met the criteria of a PR in the extended protocol. Most of the patients in this clinical study were receiving concurrent antiretroviral regimens that included protease inhibitors and/or nucleoside analogs. Although the use of antiretroviral agents has been suggested to reduce lesion progression,[30] in this study, improvement observed in the KS lesions was temporally related to initiation of docosanol 10% cream treatment. Furthermore, there was no apparent difference between responding and nonresponding patients in the type of antiretroviral regimen used. Thus, there appears to be no correlation between a patient's antiviral regimen and his response to topical docosanol 10% cream.

While we anticipated that response to treatment might be better in patients with higher T cell counts and lower viral RNA levels, the responses in this study showed no obvious correlation with either measure. In responding patients pretreatment $CD4^+$ cell numbers ranged from 34 to 549 cells/μl; viral RNA levels as determined by PCR ranged from $<$200 to 25,657 copies/ml. Similar ranges were seen in nonresponding patients. All of the responding patients had a history of prior opportunistic infections.

The effect of combination therapies including protease inhibitors on the occurrence of Kaposi's sarcoma lesions in HIV-1-positive patients remains unclear; it may be that the incidence of severe pervasive cases of cutaneous lesions that would not be amenable to topical therapy will decrease whereas milder cases with discrete lesions such as presented in this study will persist or increase. This disease presentation would ideally be treated by a nontoxic, soothing, and effective topical treatment. Systemic therapy with docosanol for KS with visceral involvement or for severe cases of cutaneous disease is not currently an option, because the insolubility of the aliphatic alcohol makes the development of aqueous formulations problematic. However, topical application provides a safe potential treatment for cases of mucocutaneous KS with discrete lesions.

Over 1000 immunocompetent patients have been safely treated with docosanol 10% cream in clinical studies of the drug's efficacy as a therapy for recurrent oral-facial herpes infections and extensive toxicology studies in doses far exceeding potential human exposure from chronic human use have not revealed any negative findings.[2–4] Likewise, no significant treatment-related adverse events were reported by any patient in this trial, suggesting that docosanol 10% cream can also be safely used in immunocompromised individuals without unde-

sirable side effects. The absence of either local or systemic adverse effects upon treatment with docosanol 10% cream contrasts dramatically with side effects of currently available treatment options.[10]

Interpretation of the study results with respect to efficacy is limited because (1) the study was an open label study with no placebo group and (2) patients continued established antiviral regimens during treatment with docosanol cream. Additionally, the study protocol did not specify use of ACTG response criteria.[31,32] Description of lesions (e.g., nodular, raised, soft, firm) was not well standardized, and important effects of treatment on the vertical dimension of the lesions may have been lost. There is, in fact, some indication (Table 2) that lesions became flatter during the treatment period in that lesions described as round or firm at baseline were described as flatter and/or softer by the 28-day visit. The study has nevertheless shown that docosanol can be used safely in immunocompromised individuals and that it may exert clinical benefits on cutaneous KS lesions in HIV-infected patients, indicating that docosanol 10% cream merits further investigation as a topical therapy for the treatment of cutaneous KS disease.

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